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REVIEW ARTICLE

Anesthetic management of the patient with amyotrophic lateral sclerosis

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Abstract Amyotrophic lateral sclerosis (ALS), with an incidence of 1.5–2.5 for 100 000 per year, is a rare but rapid progression neuromuscular degeneration disorder that poses unique perioperatively challenges to clinical anesthesiologists. The progressive degeneration of motor neurons causes a constellation of symptoms, including muscular weakness, atrophy, fasciculations, spasticity, and hyperreflexia. Therapeutic and experimental treatments, including riluzole, beta lactams, methylcobalamin, dexpramipexole, antiepileptics, antioxidant agents, neutrophin, antiinflammatory agents, and antiapoptosis drugs, are described. Newer therapies, such as neural stem cells and diaphragmatic pacing, are presented. Because of the inherent muscle weakness and associated respiratory insufficiency, certain precautions must be utilized during anesthetic care of ALS patients. In particular, certain neuromuscular agents are contraindicated and anesthetics that leave the body more rapidly present logical and attractive options in this population. A solid understanding of the disease process, therapeutic interventions, and anesthesia considerations are all paramount for the successful management of a patient with ALS in the perioperative setting.

Keywords Amyotrophic lateral sclerosis · Anesthesia · Neuromuscular degeneration disorder

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Introduction

Amyotrophic lateral sclerosis (ALS) is a rare but fatal neurodegenerative disease affecting both upper and lower motor neurons. The course of the disease is progressive and over half of the patients succumb within 3 years [1]. ALS is commonly referred to as Lou Gehrig Disease after the hall of fame baseball player who purportedly died from the disease in 1941. Though there is now evidence that he may have died from a separate but very similar neurodegenerative disease [2], Lou Gehrig still remains the poster-child for ALS. The progressive degeneration of motor neurons causes symptoms of muscular weakness, lack of coordination, atrophy, fasciculations, spasticity, and hyperreflexia [3]. ALS remains the most common form of motor neuron disease with an incidence of 1.5–2.5 for 100 000 per year. Within the ALS population, 90 % appear to be sporadic and 10 % familial; however, there is no difference in clinical presentation between the familial and sporadic forms of the disease [4]. There is no curative treatment for ALS, and all current treatment is palliative. Death usually occurs as a result of respiratory insufficiency [1]. Of the supportive therapies available, the most commonly used is riluzole, a compound that decreases the presynaptic release of glutamate, and thus decreases excitotoxicity [5]. Because of the inherent muscle weakness and associated

respiratory insufficiency, certain precautions must be taken during anesthetic care of ALS patients.

Causative factors

ALS has been associated with several derangements at the cellular level, including alterations of the cytoskeleton, mitochondrial function, microglial activation, and the metabolism of reactive oxygenating species and glutamate [6]. Some patients have also exhibited defects in the level and expression of immunoglobulin G (IgG) [7]. ALS pathogenesis is described in Fig. 1.

There are believed to be three variants of ALS: classic sporadic, familial, the majority of which exhibit autosomal dominant inheritance, and the western Pacific type, often associated with dementia [6]. Mutations in superoxide dismutase 1 (SOD1), TAR DNA-binding protein (TARDBP, also known as TDP43) and fused in sarcoma (FUS, also known as translocated in liposarcoma) have been found to contribute to 30 % of classic familial ALS. The cause of the remainder of the familial ALS and the majority of sporadic ALS is unknown. However, a recent study by Siddique et al. [8] revealed that mutations in UBQLN2, which encodes the ubiquitin-like protein ubiquilin 2, is the cause of dominantly inherited, chromosome X-linked ALS and ALS/dementia. In this particular case, abnormalities in ubiquitin 2 were linked to defects in protein degradation, abnormal protein accumulation, and subsequent neurodegeneration. Previous studies at the Skaggs Institute for Chemical Biology demonstrated that mutations in the SOD1 cluster in protein regions affect the cell's architectural integrity. Electron microscopy indicates that these mutations promote the formation of filamentous aggregates [9]. These studies imply that protein aggregation plays an integral part in familial forms of ALS.

Other proposed triggers for the development of ALS include environmental hypothesis such as bacteria and tobacco smoke. The cyanobacteria/BMAA hypothesis has been studied for years in Guamanians as there is a 100-fold increase in the incidence of ALS in the population. Research has shown a link between the presence of beta-methylamino-L-alanine (BMAA) in brain tissue and the development of ALS. BMAA is produced by symbiotic cyanobacteria on the roots of the indigent cycad trees in Guam [10]. More recently, a longitudinal study pooling the results of five prospective cohorts supported the hypothesis that cigarette smoking may increase the risk of ALS, although further investigation is warranted [11].

In the past few years, brain and spinal cord autopsy findings on athletes have linked physical injury, for example football-, soccer-, and boxing-related concussions, to the high incidence of ALS in former athletes. This has led to reforms in sports in terms of concussion testing and

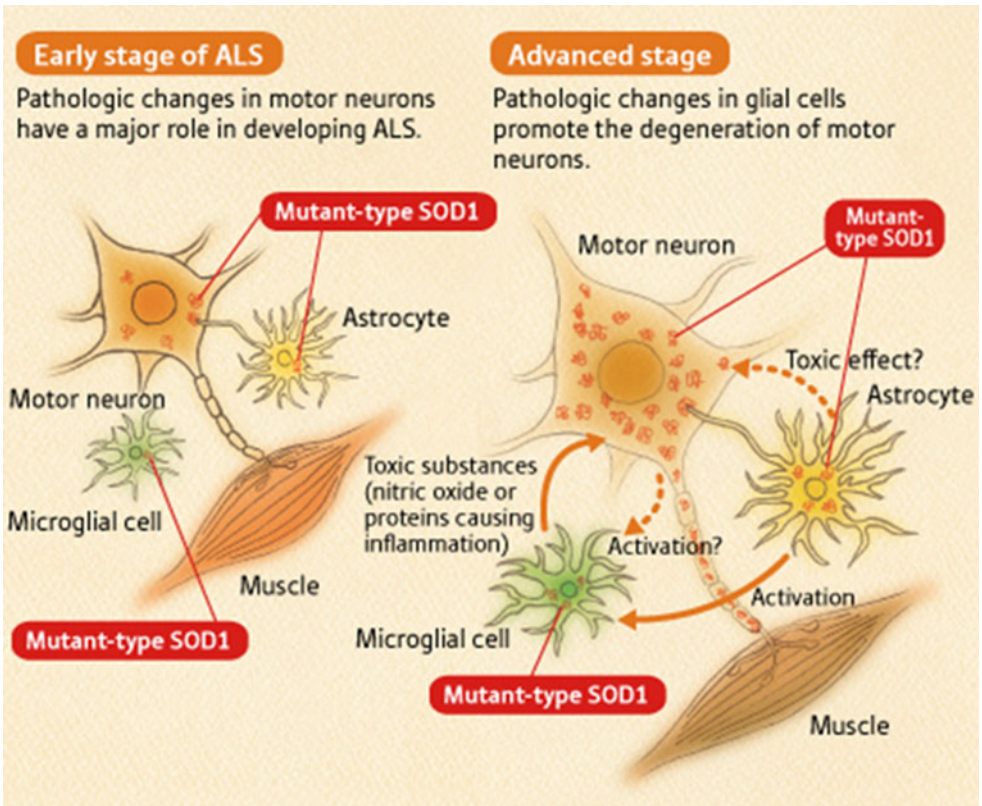

Fig. 1 Pathogenesis of ALS. Activated microglial cells release proteins that produce nitric oxide or others (cytokines) which cause inflammation, and cause damage to motor neurons and accelerating the progress of ALS. From Riken Research, Focusing on glial cells to overcome an intractable disease, ALS, 24 October 2008 (Volume 3 Issue 10). http://www.rikenresearch.riken.jp/eng/frontline/5598, accessed march 13, 2013

rest periods. Historical investigations of athletes, including Lou Gehrig, with whom ALS is most prominent linked, have found surprising documentation of repeated brain/spinal cord trauma without rest. Gehrig was known as the "Iron Horse" and played in 2130 consecutive games over a 14 year period. A recent review of archived newspapers revealed that Gehrig had over a dozen severe concussions while playing baseball in an era when batting helmets were not used and each time, he refused to take time off to heal from his concussive symptoms. Additional autopsy findings in the coming years should better link early data of brain/spinal cord injury and the development of ALS [12].

Pathophysiology

As previously mentioned, ALS is a neurodegenerative disorder affecting both upper and lower motor neurons [1]. The death of motor neurons in the brain and spinal cord lead to progressive symptoms of muscular weakness, atrophy, fasciculations, spasticity, and hyperreflexia [3]. At its onset ALS may involve selective loss of function of only upper or lower motor neurons, making it difficult to diagnose. However, the disease will ultimately cause progressive loss of both categories of motor neurons, and signs of such are required for a definitive diagnosis [1]. In order to better understand the pathophysiology behind ALS, the anesthesia provider must first have a working knowledge of the neurologic pathways involved.

The lateral corticospinal tract is responsible for propagating impulses for discrete voluntary movement from the cerebral cortex to the spinal cord, and is therefore one of the most clinically relevant pathways in the nervous system [13]. The corticospinal fibers originate in layer five of the motor cortex and descend through the internal capsule and the cerebral peduncle of the midbrain. The lateral corticospinal tract decussates in the ventrocaudal medulla and descends via the pyramidal tract in the lateral horn of the spinal cord to synapse with lower motor neurons, either directly or indirectly via interneurons [1, 13]. Another important pathway originating in the motor cortex is the corticobulbar tract. Also traveling within the internal capsule but just anterior to the corticospinal tract, the corticobulbar tract descends to the cervical spinal cord by passing through the crus cerebri medial to the corticospinal tract. The corticobulbar fibers have branches that terminate on the cervical and facial motor nuclei, nucleus ambiguus, hypoglossal nuclei, and accessory nucleus [14]. Both the corticospinal and corticobulbar tracts comprise the upper motor neurons which are involved in the pathology of ALS.

Damage to the corticospinal or corticobulbar tracts at any level will produce upper motor neuron signs. In ALS, damage to these tracts occurs from demyelination and gliosis secondary to degeneration of Betz cells located in the motor cortex [14]. Prior to the destruction of these cells, motor neurons develop proteinaceous inclusions in their cell bodies and axons. This may in part be due to defects in protein degradation [15]. Interestingly, however, these inclusions do not stain with the dyes Congo Red or Thioflavin S, and are therefore non-amyloid aggregates. Instead, these inclusions often contain ubiquitin and generally incorporate one of the ALS-associated proteins: SOD1, TARDBP, or FUS. This is in contrast to the aggregates and plaques seen in many other neurodegenerative diseases of protein aggregation, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion diseases [16, 17]. Signs typical to these upper motor neuron lesions include weakness, increased tone, spasticity, and hyperreflexia. A patient with this type of lesion may also present with pathologic reflexes such as Babinski's sign [13].

Lower motor neurons are comprised of both neurons originating in the anterior horn of the spinal cord, extending to peripheral nerves which synapse on skeletal muscle, as well as those originating in the motor cranial nerve nuclei in the brainstem. In ALS, lower motor neuron damage is secondary to massive destruction of the anterior horn cells of the spinal cord and motor cranial nerve nuclei.

Recent investigational theories

There is current evidence available that excitotoxicity may play an important role in the pathology behind ALS [18]. Several theories include decreased glutamate uptake by surrounding astrocytes, interference with mitochondrial function, impaired gamma-aminobutyric acid (GABA) inhibitory control of cortical motoneurons, and protein aggregation among many others [18, 19]. Another valid argument that excitotoxicity may play an important role is that the only drug proven to slow the disease process in humans, riluzole, possesses anti-excitotoxic properties [18].

Clinical manifestations

The initial manifestations of ALS are usually weakness or clumsiness, often beginning focally and spreading to adjacent muscle groups. However, the presentation may vary greatly depending on whether the corticospinal/corticobulbar tracts (upper motor neurons) or the lower motor neurons are more involved at the onset of the disease [14]. With a more pronounced corticospinal deficit, ALS manifests with spasticity and hyperreflexia of the extremities [12]. A deficit involving more corticobulbar fibers initially would cause dysphagia, dysarthria, and a pseudobulbar effect [1, 14].

When lower motor neurons are primarily involved, the presenting symptoms likely consist of asymmetric weakness, usually in the distribution of one extremity. Early denervation can lead to progressive weakness atrophy and fasciculations. As with upper motor neuron involvement, lower motor neuron deficits can also occur in the bulbar region. This may result in problems chewing, swallowing, and with facial movement [1].

The initial symptoms of ALS can occur in almost any muscle group. It is important to keep in mind that, although the disease process may begin asymmetrically, an increasing number of muscle groups become affected until the condition has symmetric distribution. By definition, ALS will eventually involve both upper and lower motor neurons, regardless of which predominated initially [1]. Bowel, bladder, sensory, and cognitive function all appear to remain intact despite the progressive nature of the disease [14]. Signs and symptoms of ALS associated with upper and lower motor disease are described in Table 1.

Table 1 Upper and lower motor neuron signs associated with amyotrophic lateral sclerosis

Upper motor neuron signs	Upper motor neuron symptoms
Increased reflexes (Hoffman's sign, crossed adduction, upgoing toe, distal spread of arm reflexes)	Jaw clinching/biting
	Trismus
	Spontaneous jaw clonus
Increased spasticity	Dysphagia
Facial diparesis	Dysarthria
Palmomental sign	Laryngospasm
Poor palatal elevation	Pseudobulbar effect
Slow tongue movement	Sialorrhea (drooling)
Gait disorder (spastic)	Difficulty managing pharyngeal secretions
Slowed rapid alternating movements	Limb stiffness, slowness, incoordination of movement
	Spontaneous clonus
	Spontaneous flexor spasm
	Axial stiffness/imbalance
Lower motor neuron signs	**Lower motor neuron symptoms**
Weak masseter/pterygoids	Incomplete eye closure
Difficulty maintaining jaw closure	Difficulty opening/closing the jaw
Poor palatal elevation	Poor lip closure and seal
Tongue weakness	Dysphagia
Muscle atrophy/fasciculation	Dysarthria
Intrinsic hand weakness, foot drop, proximal muscle weakness	Hoarseness
	Difficulty holding up head
Gait disorder (steppage, waddling)	Limb weakness/atrophy
Reduced reflexes	Fasciculations
Neck extension/weakness	Cramps
Truncal extension/weakness/ increased lordosis	Difficulty maintaining erect posture
Abdominal protuberance	Dyspnea/orthopnea
Tachypnea	Weak cough
Reduced vocal volume, shortened sentences	Sleep disordered breathing
Use of accessory respiratory muscles	
Abdominal paradox	

Diagnosis

The diagnosis of ALS has historically been one of exclusion with the presence of upper and lower motor neuron signs at multiple levels. Previously, diagnosis and disease progression was based upon serial monitoring of various reflexes, including the soleus stretch reflex [20]. However, recent technological advances have led to a change in perspective of how to diagnose ALS, resulting in the development of inclusive diagnostic criteria which show both good sensitivity and specificity. These include both the El Escorial criteria and more recently the Awaji criteria. Both sets of criteria are based upon the principle that neurophysiological data via EMG should be used synergistically with clinical information. The criteria are based upon three key principles, which include evidence of lower motor neuron loss, evidence of reinnervation, and fibrillation and sharp waves or fasciculation potentials. There must also be involvement of at least two muscles innervated by different roots and nerves in the cervical and lumbar-sacral region and a minimum of one muscle involved in the bulbar and thoracic regions. These criteria help to stratify patients into groups of clinically definite, clinically probable, or clinically possible ALS. Stratification then allows for the clinician to guide the management of each patient [21].

Current and new therapies

There is no curative therapy, nor is there any treatment available that is capable of completely arresting the progression of this debilitating disease. There are, however, therapeutic agents that provide both palliative relief and supportive care. These drugs are described in Table 2. Significant advances in both symptomatic and adjunctive therapies have resulted in prolonged duration and improved quality of life for patients. There is also data that supports the notion that multi-disciplinary clinics may help to prolong patient survival [22]. While the scope of FDA approved medications remains limited, there are

Table 2 Agents that are considered safe for ALS patients perioperatively with side effects

Symptom	Treatment	Side effects
Spasticity	Baclofen	Transient drowsiness, sedation, dizziness, weakness, fatigue, headache, nausea, constipation, insomnia, hypotension, asthenia
	Tizanidine	Hypotension, xerostomia, asthenia, drowsiness, dizziness, somnolence
	Benzodiazepines	Change in appetite, weight gain, constipation, reduced salivation, xerostomia, confusion, incoordination, memory impairment, sedation, irritability, fatigue
	Dantrolene	Diarrhea, asthenia, dizziness, somnolence, fatigue
Cramps	Vitamin E	Rare
	Evening primrose oil	Headache, indigestion, nausea
	Brewer's yeast	Flatulence
	Baclofen	(see above)
	Gabapentin	Peripheral edema, nausea, vomiting, viral disease, ataxia, dizziness, nystagmus, somnolence, hostile behavior, fatigue
Fasciculations	Reassurance, no treatment	
Depression	Selective serotonin reuptake inhibitors	Diaphoresis, rash, anorexia, nausea, xerostomia, asthenia, dizziness, insomnia, somnolence, tremor, impotence
Pseudobulbar effect	Selective serotonin reuptake inhibitors	(see above)
Sialorrhea	Tricyclic antidepressants	Weight gain, constipation, xerostomia, dizziness, headache, somnolence
	Dextromethorphan and quinidine	Peripheral edema, diarrhea, vomiting, asthenia, dizziness, cough
	Amitriptyline	Weight gain, constipation, xerostomia, dizziness, headache, somnolence
	Scopolamine patches	Xerostomia, somnolence, blurred vision
	Glycopyrrolate	Flushing, constipation, vomiting, xerostomia, nasal congestion
Air hunger	Parotid irradiation	N/A
	Atropine drops	Tachyarrhythmia, constipation, xerostomia, blurred vision
	Botulism toxin injections	Injection site pain, headache
	Supplemental oxygen	N/A
Only FDA approved drug for disease modification	Riluzole	Hypertension, tachyarrhythmia, circumoral paresthesia, arthralgia, asthenia, dizziness, somnolence, GI disturbances, elevated liver enzymes, vertigo, respiratory depression

several Stage 2 and 3 clinical trials in process that show promise.

Riluzole

Riluzole remains the only FDA approved medicine to both treat and prolong patient survival. Although the exact mechanism of action remains unknown, the drug is thought to preserve and protect motor neuron function by decreasing toxic glutamate levels at nerve terminals via three mechanisms [23]. These include inactivation of sodium channels, inhibiting glutamate release, and blocking post synaptic actions of NMDA receptors [24]. Several prospective, double blind, placebo controlled trials have shown an average of a 2–4 month increase in survival with about 9 % of patients having an additional year of survival [25]. Benefit has been shown for doses between 50 and 200 mg daily. While riluzole is generally well tolerated

among patients, some of the more common side effects are asthenia, dizziness, gastrointestinal disturbances, and mild elevations in hepatic enzymes. Patients who tend to have the greatest benefit from therapy are those who have a pulmonary vital capacity greater than 60 %, symptomology present for <5 years, and no tracheostomy. Even though riluzole has been shown to have little or no effect on muscle strength, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) noted that the therapy was shown to delay the need for tracheotomy by several months [26]. Subsequently in 2009, the American Academy of Neurology concluded that riluzole is both safe and effective to slow ALS progression [27].

Beta lactams

Ceftriaxone is a beta lactam antibiotic which appears to upregulate the GLT-1 glutamate transporter, also known as excitatory amino acid transporter type 2 (EEAT2), potentially correcting cellular glutamate levels. According to the NIH, the use of ceftriaxone is currently in Phase 3 clinical trials [23].

Methylcobalamin

Another potential treatment currently being investigated is high dose vitamin B12. The compound has shown promise by reducing homocysteine mediated toxicity in NSC-34 cells. This treatment remains novel and is currently in Phase 2/3 clinical trials [23].

Dexpramipexole

Dexpramipexole is the R (+) isomer of pramipexole, which is currently approved to treat both Parkinson's and restless leg syndrome. Dexpramipexole functions as an antioxidant specifically targeting the mitochondria. This enantiomer has much less affinity for dopaminergic receptors, minimizing dopaminergic effects. Preliminary studies show that the antioxidant has neuroprotective properties and is both safe and well tolerated. Cudkowicz et al. [28] have shown a dose-dependent effect on the rate of functional decline and mortality. The use of this therapy is currently being evaluated in Phase 3 clinical trials.

Experimental therapies

Antiepileptics

Gabapentin, classically used as an antiepileptic drug and in various pain therapies, is effective by decreasing the synthesis of glutamate. However, at this time the use of gabapentin has not been shown to be effective in either slowing progression of the disease or for symptomatic muscle spasm relief [29].

Antioxidants

In ALS, reactive oxygen species can be produced in abundance, leading to oxidative stress with the potential to induce neuronal damage, which in turn can cause cell death via apoptosis or necrosis [30]. The use of anti-oxidants such as vitamin E, *n*-acetylcysteine, and L-methionine have all been studied in an attempt to minimize cellular oxidative stress and slow disease progression [31]. While there has been some documented benefit in animal models, unfortunately there has been no clinical efficacy in humans [32]. One of the key problems associated with anti-oxidant therapy is breaching the blood–brain barrier [33]. Despite setbacks, research remains ongoing.

While research remains limited, one study done by Wang et al. [34] showed that, while vitamin E may not be able to slow the progression of disease, there is evidence that regular vitamin E intake may be protective and prevent disease onset altogether. This research remains novel and deserves further consideration for prospective cohort studies in the future.

Neurotrophins

Neurotrophins control the development and maintenance of the nervous system; in a mature nervous system, neurotrophins affect neuronal survival as well as influence synaptic function and plasticity [35]. Several preclinical studies have evaluated the efficacy of different factors such as insulin like growth factor-1, vascular endothelial growth factor, glial cell derived neurotrophic factor, and brain derived neurotrophic factor. Unfortunately these have failed to show any survival benefit [32, 36–39]. Difficulty remains with drug penetration through the blood–brain barrier and research to solve the issue is currently ongoing.

Anti-inflammatory agents

Neuroinflammation is a pathological hallmark in both ALS patients and mutant SOD1 animal models [32]. Previous research has shown that, in patients with ALS, COX-2 expression was dramatically increased in the spinal cord, motor neurons, interneurons, and glial cells [40]. Administration of celecoxib, a selective COX-2 inhibitor, was actually shown to prolong survival in SOD1 mutant mice by anywhere from 12 to 28 days [32, 41]. However, subsequent human studies done by Cudkowicz et al. [42] showed celecoxib failed to demonstrate any efficacy in a randomized, double-blind, placebo trial of 300 patients with ALS.

Antiapoptotics

In mutant SOD1 mice, research has found that motor neuron death occurs by apoptosis mediated by sequential activation of caspase-1 and 3 [32, 43]. Minocycline, a second generation tetracycline antibiotic that both crosses the blood–brain barrier and indirectly inhibit caspase-1 and 3 was shown to delay symptom onset in mutant SOD1 mice [32, 44]. However, a multicenter, Phase 3, randomized, controlled trial of minocycline failed to show any benefit in 400 ALS patients [44].

Diaphragmatic pacing systems (DPS)

Diaphragmatic pacing systems have previously been used to successfully treat spinal cord injured patients, with multicenter trials showing 98 % of DPS patients being liberated from ventilatory support [45–47]. This success led to FDA approval for DPS use in spinal cord injury patients and further investigation to see if there was any benefit for ALS patients. The goal behind DPS is to preserve diaphragm strength, decreasing the rate of loss of FVC, and prolonging the onset of mechanical ventilation dependency or tracheotomy [48]. DPS involves laparoscopic mapping of the motor point of each hemi-diaphragm to identify the optimal point of stimulation resulting in maximal contraction of the diaphragm [48]. This stimulation theoretically improves respiratory efforts by converting diaphragm muscle from fast type IIB to slow twitch type 1 [48]. While there has been some documented benefit, more research is needed before DPS can be routinely recommended to slow respiratory decline and preserve function in ALS patients.

Treatment of emotional labiality

Pseudobulbar effect is a consequence of bilateral corticobulbar tract degeneration and may affect approximately half of all ALS patients [49]. Pseudobulbar effect is a term that encompasses sudden uncontrollable bouts of laughter or crying that occur often inappropriate to the context of the situation. A drug combination of dextromethorphan–quinidine has been FDA approved for these symptoms [50].

Use of multi-disciplinary clinics

ALS is a progressive and terminal disease and maximizing patient care is often multi-faceted and complex. As disease progression occurs, close attention must be paid to a patient's nutritional, respiratory, and functional status. This complexity has resulted in the development of all encompassing multi-disciplinary clinics and there has been data that suggest patients cared for at multi-disciplinary clinics may survive longer [51, 52]. Care teams may consist of a neurologist, specific ALS nurses, physical therapists, a gastroenterologist to monitor nutritional status, a pulmonologist to monitor respiratory decline, and social workers to help with associated bills and insurance. Centers like these help to ensure that patients maintain the highest quality of life throughout the progressive and debilitating disease course [51].

Anesthetic/surgical considerations and management

Due to the progressive nature of the disease, ALS patients will invariably undergo various surgical procedures for both symptomatic and palliative care. These most commonly include: percutaneous enteral gastrostomy feeding tube placement, long term line placement for infection or aspiration complications, and tracheotomy. There is a limited amount of literature pertaining to the anesthetic management of ALS. Despite this, anesthetic management should still encompass the three main components of any anesthetic case, including preoperative, intraoperative, and postoperative management. Preoperative assessment should include pulmonary function testing to assess functional vital capacity, as this is a key indicator to successful extubation postoperatively [48]. Reduced pulmonary function tests can be a red flag for a patient with a higher likelihood of postoperative respiratory issues. Some of these tests include inspiratory capacity, negative inspiratory force, and/or vital capacity. The American Academy of Neurology's practice parameter is that ALS patients with an FVC <50 % should be offered non-invasive positive pressure ventilation [48, 53]. Advanced bulbar symptoms increase the risk of aspiration and respiratory inadequacy. Intraoperatively, the goal is to use rapid reversible short-acting analgesic and amnestic agents [48]. Onders et al. [48] describe successful intraoperative management in ALS patients using this methodology. Propofol and remifentanil infusion should be used for induction and are generally considered safe and ideal. Remifentanil is ideal due to its ultra short acting nature. Though there is limited data, inhalational agents can be utilized with the caveat being that there is a potential for postoperative respiratory depression and that extubation should be done with the patient fully awake. Of the most common inhalational agents available, isoflurane has moderate lipid solubility and a slower recovery time when compared with desflurane and sevoflurane. Therefore, desflurane and sevoflurane are preferred for maintenance due to their low lipid solubility allowing for rapid reversal and dose adjustment [48]. Depolarizing neuromuscular blockers, such as succinylcholine, act as acetylcholine agonists.

These agents should be *strongly avoided* because they can cause a lethal elevation of serum potassium in neuromuscular disorders like ALS [54]. Muscle relaxants should also be used sparingly and at the lowest possible doses. In cases where a nondepolarizer is utilized, it is paramount to monitor with an electrical twitch monitor. Nondepolarizing neuromuscular blockers act as competitive antagonists of the post synaptic receptor. Acetylcholine is prevented from binding to its receptor, thus producing flaccid paralysis. There have been several case reports detailing the successful use of rocuronium in ALS patients undergoing general anesthesia [55]. However, nondepolarizing agents should be used with caution as these agents can result in prolonged weakness. In this scenario, sugammadex given at the dose of 2 mg/kg intravenously has been shown to expedite paralytic reversal safely and efficiently [55]. Postoperatively, close attention to the respiratory status is paramount as many ALS patients already have a compromised respiratory state. Those on NPPV preoperatively should be placed back on NPPV postoperatively [48].

Finally, peripheral nerve blocks and various local or regional techniques to help both intraoperatively and to assist in managing postoperative pain management have been successful in clinical practice for this patient population [56–58]. However, there is a general concern about the use of regional anesthesia and disease exacerbation [59]. Routine postoperative use of oxygen should be limited because ALS patients have an inherent instability of respiratory control and their drive for respirations when sleeping is based on oxygen saturation. In this regard, if a patient becomes confused, an arterial blood gas reading should be obtained to ensure the patient is not becoming hypercarbic [48]. As mentioned earlier, thorough preoperative assessment of pulmonary function will aid the clinician when weaning from mechanical ventilation given that each of these patients have some degree of pulmonary pathogenesis and limited functional reserve. A careful balance between safety and comfort is critical. ALS patients have reduced neurophysiological reflexes and responses. Therefore, conservative dosing of opiates in particular with enhanced postoperative monitoring such as pulse oximetry can optimize postoperative pain management and minimize morbidity and mortality.

In summary, when considering anesthetic management in ALS patients, careful monitoring and appropriate drug selection is obligatory. In neuromuscular disorders like ALS, the release of potassium can be markedly increased; depolarizing neuromuscular blockers such as succinylcholine should be avoided because they can cause an exaggerated elevation of serum potassium. Muscle relaxants should also be used sparingly and at the lowest possible doses. Because of the patient's susceptibility to respiratory distress, postoperative ventilatory support is absolutely indicated. Successful management of ALS patients requires a collaborative perioperative effort from all healthcare professionals involved in the patients care.

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References

1. Brown RH. Amyotrophic lateral sclerosis and other motor neuron diseases. In: Longo DL, Kasper DL, Fauci AS, Hauser SL, Jameson JL, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill Medical Publishing Division; 2011. p. 3345–51.
2. McKee AC, Gavett BE, Stern RA. TDP-43 Proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol. 2010;69(9):918–29. doi:10.1097/NEN.0b013e3181ee7d85.
3. Gordon PH, Mitsumoto H, Hays AP. Amyotrophic lateral sclerosis. Sci Aging Knowl Environ. 2003;. doi:10.1126/sageke.2003.35.dn2.
4. Soriani MH, Desnuelle C. Epidemiology of amyotrophic lateral sclerosis. Rev Neurol (Paris). 2009;165(8–9):627–40. doi:10.1016/j.neurol.2009.04.004.
5. Marsh JS, Johnson KK, Hoover JM, Kaye AD. Preanesthetic assessment of the patient with amyotrophic lateral sclerosis. Anesthesiol News. 2004;30(9):47–50.
6. Strong M, Rosenfeld J. Amyotrophic lateral sclerosis: a review of current concepts. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4(3):136–43.
7. Bach JR. Management of patients with neuromuscular disease. Philadelphia: Hanley & Belfus, Inc; 2004. p. 25, 33–35, 69, 341, 348.
8. Siddique T, et al. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature. 2011;. doi:10.1038/nature10353.
9. Didonato M, Craig L, Huff ME, Thayer MM, Cardoso R, Kassmann CJ, Lo TP, Bruns CK, Powers ET, Kelly JW, Getzoff ED, Tainer JA. ALS mutants of human superoxide dismutase form fibrous aggregates via framework destabilization. J Mol Biol. 2003. doi:10.1016/S0022-2836(03)00889-1.
10. Bradley WG, Mash DC. Beyond Guam: the cyanobacteria/BMAA hypothesis of the cause of ALS and other neurodegenerative diseases. Amyotroph Lateral Scler. 2009;. doi:10.3109/17482960903286009.
11. Wang H, O'Reilly EJ, Weisskopf MG, Logroscino G, McCullough ML, Thun M, Schatzkin A, Kolonel L, Ascheria A. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of five prospective cohorts. Arch Neurol. 2011;. doi:10.1001/archneurol.2010.367.
12. Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012;. doi:10.1212/WNL.0b013e31826daf50.
13. Blumfeld H, editor. Neuroanatomy through clinical cases. Sunderland: Sinayer Associates, Inc; 2002. p. 220–225, 243, 256–259.
14. Hallum A, Allen DD. Neuromuscular diseases, Chapter 17. In: Umphred DA, Burton GU, Lazaro RT, Roller ML, editors. Neurological rehabilitation. 6th ed. St. Louis: Mosby-Year Book; 2013. p. 521–71.
15. Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, Yang Y, Fecto F, Shi Y, Zhai H, Jiang H, Hirano M,

Rampersaud E, Jansen GH, Donkervoort S, Bigio EH, Brooks BR, Ajroud K, Sufit RL, Haines JL, Mugnaini E, Pericak-Vance M, Siddique T. Mutations in UBQLN2 cause dominant X-linked juvenile and adult onset ALS and ALS/dementia. Nature. 2011;. doi:10.1038/nature10353.
16. Kwong LK, Uryu K, Trojanowski JQ, Lee VM. TDP-43 proteinopathies: neurodegenerative protein misfolding diseases without amyloidosis. Neurosignals. 2008;. doi:10.1159/000109758.
17. Kerman A, Liu HN, Croul S, Bilbao J, Rogaeva E, Zinman L, Robertson J, Chakrabartty A. Amyotrophic lateral sclerosis is a non-amyloid disease in which extensive misfolding of SOD1 is unique to the familial form. Acta Neuropathol. 2010;. doi:10.1007/s00401-010-0646-5.
18. Van Den Bosch L, Van Damme P, Bogaert E, Robberecht W. The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis. Biochimica et Biophysica Acta. 2006. doi:10.1016/j.bbadis.2006.05.002.
19. Vande Velde C, Cleveland DW. Amyotrophic lateral sclerosis (ALS): disease mechanisms. Encycl Neurosci. 2008;369–373.
20. Christensen PB, Nielsen JF, Sinkjaer T. Quantification of hyperreflexia in amyotrophic lateral sclerosis by the soleus stretch reflex. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4:106–11.
21. Costa J, Swash M, de Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis: a systematic review. Arch Neurol. 2012;. doi:10.1001/archneurol.2012.254.
22. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of multi-disciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neursurg Psychiatry. 2003;. doi:10.1136/jnnp.74.9.1258.
23. Pratt AJ, Getzoff ED, Perry JJP. Amyotrophic lateral sclerosis: update and new developments. Degener Neurol Neuromuscul Dis. 2012;. doi:10.2147/DNND.S19803.
24. Doble A. The pharmacology and mechanism of action of riluzole. Neurology. 1996;47(6 Suppl 4):S233–41.
25. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for ALS/motor neuron disease. Cochrane Database Syst Rev. 2007;. doi:10.1002/14651858.CD001447.
26. Practice advisory on the treatment of amyotrophic lateral sclerosis with riluzole: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 1997. doi:10.1212/WNL.49.3.657.
27. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J, Shoesmith C, Strong MJ, Woolley SC. Practice parameters update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;. doi:10.1212/WNL.0b013e3181bc0141.
28. Cudkowicz M, Bozik ME, Ingersoll EW, Miller R, Mitsumoto H, Shefner J, Moore DH, Schoenfeld D, Mather JL, Archibald D, Sullivan M, Amburgey C, Moritz J, Gribkoff VK. The effects of dexpramipexole in individuals with amyotrophic lateral sclerosis. Nat Med. 2011;. doi:10.1038/nm.2579.
29. Baldinger R, Katzberg HD, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews 2012. Issue 4. Art. No.: CD004157. doi:10.1002/14651858.CD004157.
30. Di Matteo V, Esposito E. Biochemical and therapeutic effects of antioxidants in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Curr Drug Targets CNS Neurol Disord. 2003;2:95–107.
31. Orrell RW, Lane RJ, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Neuromuscular Disease Group. 2010. doi:10.1002/14651858.CD002829.pub4.
32. Brooks BR. Managing amyotrophic lateral sclerosis: slowing disease progression and improving patient quality of life. Ann Neurol. 2009;. doi:10.1002/ana.21544.
33. Barber SC, Mead RJ, Shaw PJ. Oxidative stress in ALS: a mechanism of neurodegeneration and a therapeutic target. Biochim Biophys Acta. 2006. doi:10.1016/j.bbadis.2006.03.008.
34. Wang H, O'Reilly EJ, Weisskopf MG, Logroscino G, McCullough ML, Schatzkin A, Kolonel LN, Ascherio A. Vitamin E intake and risk of ALS: a pooled analysis of data from 5 prospective cohort studies. Am J Epidemiol. 2011;. doi:10.1093/aje/kwq416.
35. Dawbarn D, Allen SJ. Neurotrophins and neurodegeneration. Neuropathol Appl Neurobiol. 2003;. doi:10.1046/j.1365-2990.2003.00487.x.
36. Nayak MS, Kim YS, Goldman M, Keirstead HS, Kerr DA. Cellular therapies in motor neuron diseases. Biochim Biophys Acta. 2006. doi:10.1016/j.bbadis.2006.06.004.
37. Bongioanni P, Reali C, Sogos V. Ciliary neurotrophic factor(CNTF) for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Neuromuscular Disease Group. 2004. doi:10.1002/14651858.CD004302.pub2.
38. A controlled trial of recombinant methionyl human BDNF in ALS: the BDNF Study Group(Phase III). Neurology. 1999;52:1427–1433. doi:10.1212/WNL.52.7.1427.
39. Mitchell JD, Wokke JH, Borasiio GD. Recombinant human insulin-like growth factor I (rhIGF-1) for ALS/motor neuron disease. Cochrane Neuromuscular Disease Group. 2012. doi:10.1002/14651858.CD002064.pub3.
40. Maihofner C, Probst-Cousin S, Bergmann M, Neuhuber W, Neundorfer B, Heuss D. Expression and localization of cyclooxygenase-1 and -2 in human sporadic amyotrophic lateral sclerosis. Eur J Neurosci. 2003;. doi:10.1046/j.1460-9568.2003.02879.x.
41. Drachman DB, Frank K, Dykes-Hoberg M, Teismann P, Almer G, Przedborski S, Rothstein JD. Cyclooxygenase-2 inhibition protects motor neurons and prolongs survival in a transgenic mouse model of ALS. Ann Neurol. 2002;. doi:10.1002/ana.10374.
42. Cudkowicz ME, Shefner JM, Schoenfeld DA, Zhang H, Andreasson KI, Rothstein JD, Drachman DB. Trial of celecoxib in ALS. Ann Neurol. 2006;. doi:10.1002/ana.20903.
43. Pasinelli P, Housewart MK, Brown RH Jr, Cleveland DW. Caspase-1 and -3 are sequentially activated in motor neuron death in Cu, Zn superoxide dismutase-mediated familial amyotrophic lateral sclerosis. Proc Natl Acad Sci USA. 2000;. doi:10.1073/pnas.240305897.
44. Gordon PH, Moore DH, Gelinas DF, Qualls C, Meister ME, Werner J, Mendoza M, Mass J, Kushner G, Miller RG. Placebo-controlled phase I/II studies of minocycline in ALS. Neurology. 2004;. doi:10.1212/01.WNL.0000125321.92112.7E.
45. DiMarco AF, Onders RP, Ignagni A, Kowalski KE, Mortimer JT. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest. 2005;. doi:10.1212/WNL.52.7.1427.
46. Onders RP, Ignagni AI, DiMarco AF, Ignani AR, Mortimer JT. The learning curve of investigational surgery: lessons learned from the first series of laparoscopic diaphragm pacing for chronic ventilator dependence. Surg Endosc. 2005;19:633–7. doi:10.1007/s00464-004-8934-6.
47. Onders RP, Elmo MJ, Ignagni AR. Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. J Spinal Cord Med. 2007;30:25–9.
48. Onders RP, Carlin AM, Elmo M, Sivashankaran S, Katirji B, Schilz R. Amyotrophic lateral sclerosis: the Midwestern surgical experience with the diaphragm pacing stimulation system shows

that general anesthesia can be safely performed. Am J Surg. 2009. doi:http://dx.doi.org/10.1016/j.amjsurg.2008.11.008.
49. Gallager JP. Pathologic laughter and crying in ALS: a search for their origin. Acta Neurol Scand. 1989;80:114.
50. Pioro EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, Hepner A, Kaye R. Dextromethorphan plus ultra low dose quinidine reduces pseudobulbar affect. Ann Neurol. 2010;. doi:10.1002/ana.22093.
51. Gordon PH. Amyotrophic lateral sclerosis pathophysiology, diagnosis, and management. CNS Drugs. 2011;. doi:10.2165/11586000-000000000-00000.
52. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multi-disciplinary amyotrophic lateral sclerosis clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosrug Psychiatry. 2003;. doi:10.1136/jnnp.74.9.1258.
53. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J, Shoesmith C, Strong MJ, Woolley SC. Practice parameter: the care of the patient with ALS (an evidence-based review) report of the Quality Standard Subcommittee of the American Academy of Neurology. Neurology. 2009;. doi:10.1212/WNL.0b013e3181bc01a4.
54. Bambrink AM, Kirsch JR. Perioperative care of patients with neuromuscular disease and dysfunction. Anesthesiol Clin. 2007. doi:http://dx.doi.org/10.1016/j.anclin.2007.05.005.
55. Kelsaka E, Karakaya D, Zengin EC. Use of sugammadex in a patient with amyotrophic lateral sclerosis. Med Princ Pract. 2013;. doi:10.1159/000343168.
56. Kowalik MM, Smiatacz T, Pajuro R, Skowroński R, Trocha H, Nyka W, Raczyńska K, Wujtewicz M. Anesthesia for ophthalmological surgical procedures in a patient with advanced amylotrophic lateral sclerosis: a case report. Cases J. 2008;. doi:10.1186/1757-1626-1-338.
57. Hobaika AB, Neves BS. Combined spinal-epidural block in a patient with amylotrophic lateral sclerosis: a case report. Rev Bras Anesthesiol. 2009. doi:10.1590/S0034-70942009000200008.
58. Sertöz N, Karaman S. Peripheral nerve block in a patient with amyotrophic lateral sclerosis. J Anesth. 2012. doi:10.1007/s00540-011-1268-3.
59. Bromberg TA, Boortz-Marx RL. Amyotrophic lateral sclerosis. In: Fleisher L, editor. Essence of anesthesia practice, vol. 15. 3rd ed. Philadelphia: Elsevier; 2011.